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基于数据挖掘的青光眼动物模型的应用特点分析

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【摘要】 目的 研究青光眼动物模型应用情况,为其动物实验方法和模型完善提供参考。**方法** 以“青光眼”和“动物模型”为主题词,在中国知网、PubMed 中收集 2012 年 11 月 1 日 ~ 2022 年 11 月 2 日青光眼动物模型的相关文献,总结实验动物种类、性别、造模方法、检测指标等,建立数据库进行统计分析。**结果** 共筛选得到符合标准的 400 篇文献,其中实验动物多为 C57BL/6J 小鼠,动物性别以雄性居多;造模方法多采用前房注射物质诱导型、转基因型和激光光凝诱导型;高频检测指标主要包括眼压测量、组织病理、蛋白免疫印迹和免疫组化。**结论** 目前青光眼动物模型造模方法种类较多,但是相关中医因素干预较少,建议增加病证结合的青光眼动物模型。本研究通过对青光眼动物模型实验进行挖掘分析,对不同动物模型进行评估,通过挖掘内容为构建造模成功率高、重现性好、与临床吻合度高的动物模型提供参考,为模型完善提供思路。

【关键词】 青光眼动物模型;数据挖掘;造模要素;应用分析
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Application and characteristics of a glaucoma animal model based on data mining

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【Abstract】 Objective To study the application of an animal model of glaucoma and provide a reference for improved animal experimental method and models. **Methods** We searched the CNI and PubMed databases using the terms “glaucoma ”and “animal models” to identify studies related to animal models of glaucoma from 2012 to 2022. The study species, sex, modeling method , and detection indexes were summarized, and a database was established for statistical analysis. **Results** In total, 400 articles conforming to the criteria were selected. Most of the experimental animals were C57BL/6J mice and most of them were male. The most common modeling method were anterior chamber injection-induced, transgenic, and laser photocoagulation-induced models. The most frequent detection indicators included intraocular pressure measurement, histopathology, Western Blot analysis, and immunohistochemistry. **Conclusions** Numerous method have been used to construct glaucoma animal models, but the intervention of related traditional Chinese medicine factors is less. It is suggested to increase the glaucoma animal model combined with disease and syndrome. This study evaluated different animal models of glaucoma by data mining to provide references for the construction of animal models with high modelling-success rates, good reproducibility, and high clinical coincidence, as well as providing ideas for model improvement.

【Keywords】 animal model of glaucoma; data mining; moulding element; application analysis
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青光眼是一种视神经头改变、视网膜神经节细胞(retinal ganglion fine the cell, RGC)逐渐死亡、视野丧失的进行性神经病变。眼压升高是主要的危险因素[1]。青光眼是一种发病原因复杂的高致盲性眼病。全球 40 ~ 80 岁人群中青光眼患病率为 3.5%,随着老年人在人口中的数量和比例不断增加,预计到 2040 年将有 1.118 亿人患有青光眼[2]。目前,青光眼尚无根治方法,所有的治疗方法都以降低眼压(intraocular pressure, IOP)为目标[3]。降低眼压是该病目前唯一可行的治疗方法[4]。西医对青光眼的发病机制尚未明确,中医将其归属为“五风内障”的范畴,认为该病发病与情志等多因素相关[5]。青光眼致盲给患者带来了巨大的疾病负担和经济负担。因此研究有效的治疗方法和药物至关重要,而理想的动物模型是进一步研究青光眼的重要工具。本文通过对青光眼动物模型进行归纳总结分析,为青光眼动物模型的完善提供思路,以便能更好地应用于后续的研究中。

1 资料与方法

1.1 数据来源

在中国知网、PubMed 中以“青光眼”“动物模型”为主题词进行检索,锁定检索年限 2012 年 11 月 1 日~2022 年 11 月 2 日的期刊文献建立数据库,共检索出 1088 篇文献。

1.2 纳入标准

选择“青光眼”动物模型应用研究相关的实验性文献,筛选造模方法完整及实验过程清晰的文章,最终筛选得到符合标准的 400 篇文献。

1.3 排除标准

排除造模方法不全;会议、报纸、硕博士学位论文、综述等文献及青光眼相关体外实验。

1.4 数据规范

实验动物名称、种类等均参照《实验动物和动物实验技术》[6]进行规范总结。

1.5 数据处理及分析

将纳入标准的 400 篇文献的实验动物种类、性别、造模方法、检测指标等数据录入 Excel 表,建立青光眼动物模型数据库。使用 Excel 2019 进行统计学处理与分析。

2 结果

2.1 青光眼模型动物种系应用情况

将涉及青光眼动物模型的 400 篇文献中的实验动物进行分类,总频次为 400。总共 24 类动物,最多的为 C57BL/6J 小鼠(86 次;21.50%)、SD 大鼠(58 次;14.50%)、DBA/2J 小鼠(49 次;12.25%),具体见图 1。

本研究中,通过统计得到青光眼造模动物主要为鼠类。主要原因是:啮齿类动物的眼睛和人类的眼睛有许多重要的生物学相似性[7]。其中小鼠占比较高。研究表明 C57BL/6J 小鼠的视网膜更易损伤,视网膜厚度减少,血管损伤更严重[8]。DBA/2J 小鼠青光眼模型是一种近交系,随着年龄的增长逐渐发展为青光眼样异常。在前房,小鼠出现一种色素分散综合征,其主要作用是炎症反应,导致眼压升高。DBA/2J 小鼠有两种不同的表型:虹膜色素分散(可能与 DBA/2J 眼睛的免疫功能障碍有关)和虹膜色素转移(可能与虹膜色素转移有关)[9]。

2.2 青光眼模型动物性别分布情况

将 400 篇文献中所涉及的实验动物性别进行分类规范,统计得出模型动物性别分布,有 38 例未对动物性别做出标记,明确标明性别的雄性动物 150 例、占 37.50%;雌雄各半动物 90 例、占 22.50%;雌性动物 67 例、占 16.75%;雌雄不限动物 55 例、占 13.75%。上述结果显示,动物性别以雄性居多,Ha 等[10]研究发现雄激素睾酮可能与青光眼的发病机制有关。

2.3 青光眼模型造模方法

统计 400 篇文献中使用的青光眼模型造模方法,共有 12 种造模方法。前房注射物质诱导型(127 次;31.75%),转基因型(104 次;26.00%)、激光光凝诱导型(56 次;14.00%)最多。前房注射物质诱导型以微球注射前房(90 次;22.50%)、水凝胶注射(25 次;6.25%)较多;激光光凝诱导型以氩激光光凝小梁网(30 次;7.50%)、二极管激光光凝角巩膜缘和上巩膜静脉(18 次;4.50%)较多。详细造模情况见表 1。

从造模方法选择方面,前房注射物质诱导型为使用最多的方法,其中以微球注射前房最多,其次为转基因型、激光光凝诱导型。眼压升高是青光眼的主要危险因素,因此开发和使用眼压升高的动物模型进行青光眼研究是有意义的。在前房注入聚苯乙烯微珠(微球),是导致眼压升高、房水流出的主要物理阻塞[28]。DBA/2J 小鼠和其他转基因模型与人类青光眼有许多相似之处,不同个体眼压升高、视网膜和视神经损伤的反应较为一致,个体差

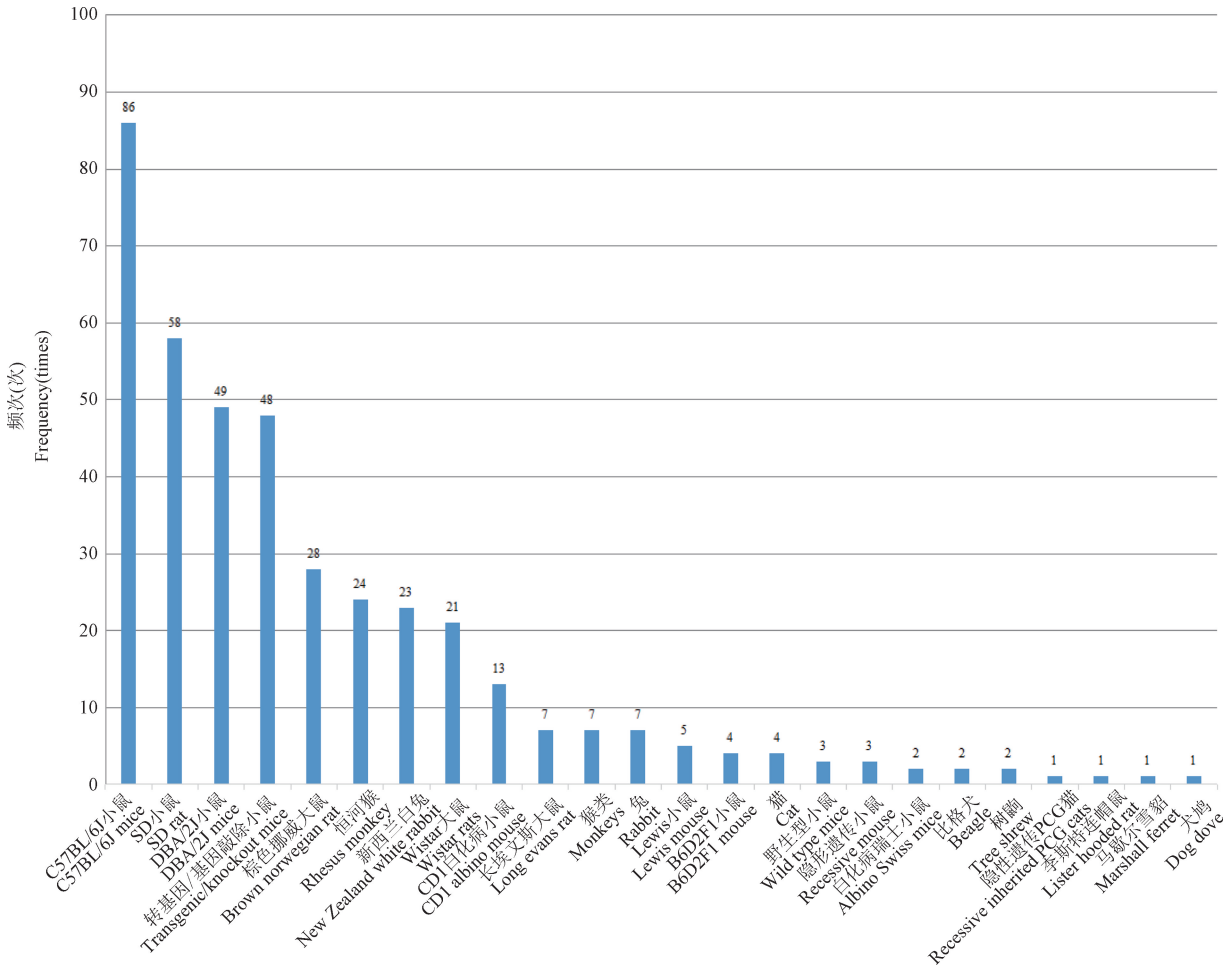

图 1　青光眼动物模型实验动物种类及频次

Figure 1　Species and frequency of experimental animals in animal model of glauco

表 1　青光眼动物模型造模方法及频次

Table 1　Method and frequency of animal model of glaucoma

造模类型 Mold type	造模方法 Molding method	造模周期(周) Molding cycle (weeks)	频数(次) Frequency (times)	文献占比(%) Literature ratio (%)
前房注射物质诱导型 Anterior chamber injection induced type	前房注射 2 μL 粒径为 6 μm 聚苯乙烯微球和 1 μL 透明质酸钠[11] 2 μL 6 μm polystyrene microspheres and 1 μL sodium hyaluronate were injected into the anterior chamber[11]	8	90	22.50
	将由 HyStem 和 Extralink 以 4∶1的比例组成的 7 μL 水凝胶注入前房[12] A 7 μL hydrogel composed of HyStem and Extralink in a 4∶1 ratio was injected into the anterior chamber[12]	4	25	6.25
	每眼先用微量进样器抽取房水,随后注射复方卡波姆溶液缓慢进入前房[13] Aqueous humor was extracted from each eye with a microsampler, followed by injection of compound carbomer solution into the anterior chamber slowly[13]	4	10	2.50
	无菌盐水中制备的新鲜 α-胰凝乳蛋白酶溶液,通过套管灌入后房[14] Fresh α-chymotrypsin solution prepared from sterile saline solution was injected into the posterior chamber through a cannula[14]	2	2	0.50

续表 1

造模类型 Mold type	造模方法 Molding method	造模周期(周) Molding cycle (weeks)	频数(次) Frequency (times)	文献占比(%) Literature ratio (%)
转基因型 Transgene type	DBA/2J 小鼠在 8 ~ 9 月龄开始出现视网膜神经节细胞凋亡和视神经的变性。18 月龄时,90% 以上的视神经严重变性及视功能丧失[15] The apoptosis of retinal ganglion cells and degeneration of optic nerve began in DBA/2J mice at 8 ~ 9 months of age. At 18 months of age, more than 90% of the optic nerve had severe degeneration and loss of visual function[15]	36	104	26.00
激光光凝诱导型 Laser photocoagulation induction type	氩激光光凝小梁网中段 60 ~ 150 处,首次光凝 2 周后,对眼压低于 30 mmHg 剩余的小梁网部分再次进行激光光凝[16] Argon laser photocoagulation was performed at 60 ~ 150 points in the middle part of the trabecular network. After 2 weeks of initial photocoagulation, laser photocoagulation was performed again on the remaining trabecular network with intraocular pressure below 30 mmHg[16]	24	30	7.50
	接受二极管激光光凝角巩膜缘和上巩膜静脉[17] Receiving diode laser photocoagulation of cornescleral margin and superior scleral vein[17]	4	18	4.50
	诱导角膜缘和 3 个巩膜外静脉光凝[18] Photocoagulation of limbus cornea and three external scleral veins was induced[18]	4	8	2.00
巩膜上静脉高渗盐水注射诱导型 Supraceral vein hypertonic saline injection induced type	选择较大、分支少的上巩膜静脉,将其与巩膜分离后,插入一个连接注射器的玻璃微针,缓慢注射高渗盐水 50 μL 到巩膜上静脉以硬化小梁网[19] The superior scleral vein with large size and few branches was separated from the sclera, and a glass microneedle connected to a syringe was inserted to slowly inject hypertonic saline 50 μL into the superior scleral vein to harden the trabecular network[19]	4	28	7.00
巩膜上静脉烙闭诱导型 Supraceral vein cautery induction type	充分暴露巩膜上静脉,烧灼静脉主干使静脉封闭[20] The supraceral vein is fully exposed and the main vein is cauterized to seal the vein[20]	4	19	4.75
滤过手术模型 Filter operation model	小梁切除术、全层巩膜咬切术、植管手术[21] Trabeculectomy, scleral bite and tube grafting[21]	4	17	4.25
视网膜缺血/再灌注损伤诱导型 Retinal ischemia/reperfusion injury induced type	注射内皮素-1 2.5 nmol/L 或选择性结扎大鼠眼血管[22] The eye vessels of rats were injected with endothelin-1 at 2.5 nmol/L or ligation selectively[22]	48 h	15	3.75
遗传型 Genotype	常染色体隐性遗传病,多在 9 ~ 18 个月大时发病[23] Autosomal recessive genetic disease, most in 9 ~ 18 months of age when the onset[23]	36	8	2.00
环角巩膜缘缝合诱导型 Annular horn scleral suture induction type	用尼龙缝合线在眼球赤道部周围的结膜上进行环形缝合,不穿透巩膜,打一个活结将缝合线系紧,通过调节活结的松紧度调整眼压[24] A circular suture is made on the conjunctiva around the equator of the eyeball with nylon sutures, without penetrating the sclera. A slipknot is tied to tighten the sutures, and the pressure is adjusted by adjusting the tightness of the slipknot[24]	2	7	1.75
视神经机械损伤诱导型 Optic neuromechanical injury induction type	视神经横断或挤压模型[25] Optic nerve transection or compression model[25]	4	7	1.75
类固醇药物诱导型 Steroid-induced	局部或全身使用类固醇药物[26] Topical or systemic use of steroid medications[26]	4	6	1.50
玻璃体内注射兴奋性毒性物质 Vitreous injection of excitatory toxic substances	注射谷氨酸、N-甲基天冬氨酸、内皮素-1 等[27] Glutamic acid, N-methyl aspartic acid, endothelin-1 and so on were injected[27]	4	6	1.50

异较小。而且转基因动物有助于识别各基因之间的相互作用[29]。激光光凝诱导型以与氩激光光凝小梁网、二极管激光光凝角巩膜缘和上巩膜静脉较多。相比氩激光,二极管激光产生更深更大的斑尺寸病变,导致小梁网损伤更大,眼压升高明显[30]。巩膜上静脉高渗盐水是以硬化小梁网,增加房水流出阻力,从而达到升高眼压的作用,但是此方法操作难度大,眼压升高不稳定,需要重复注射[31]。巩膜上静脉烙闭诱导型比激光光凝法侵入性更小,且不会引起前房并发症。由于具有的其有效性和可及性,实验性青光眼的大多数结构和功能研究都使用了这种方法。该模型中的眼压升高被认为涉及到流出阻力增加[32]。环角巩膜缘缝合是一种简单、微创、经济有效的造模方法,可诱导大鼠和小鼠的眼压升高,损伤神经节细胞[33]。前房穿刺法与植管法均能成功建立大鼠青光眼滤过手术动物模型,且植管法更有利于观察滤过泡形态及瘢痕形成情况,也可用于青光眼术后抗瘢痕相关研究[34]。视神经损伤模型是引起 RGCs 凋亡的青光眼研究常用的动物模型。它可以在模拟视神经损伤的病理变化的同时,不影响视网膜动脉、静脉功能和血液供应[35]。类固醇诱导的高眼压青光眼动物模型价格低廉且无创,但是与人类解剖学有差异[36]。各种自发性青光眼模型前后已经在不同的动物物种中被描述过。这些动物物种包括兔子、狗、猴子、小鼠、大鼠和猫。被研究的这些模型为青光眼的病理生理学提供了有价值的信息[37]。

2.4　青光眼动物模型检测指标

统计纳入标准的 400 篇文献中青光眼动物模型的检测指标,若检测指标为同一个组织的多个同类型指标,则归为一类,不再分开统计,如血清中同时检测 CRP、PCT、IL-1 和 IL-6 水平等,则把这些指标统称为血清指标,同一实验只计入一次。统计结果表明,400 篇实验文献涵盖种不同的指标类型,累计频数 818 次。其中检测较多的指标为眼压测量、组织病理(视网膜、视神经、眼球、房角)、蛋白质印迹分析(视网膜、眼睛、视网膜神经节、β-肌动蛋白、免疫球蛋白 G、RhoA、ROCK、Caspase-3)、免疫组化(视网膜、视网膜视神经节、视神经、眼睛、脑、纤连蛋白、α 平滑肌肌动蛋白)、RGCs 计数、实时荧光定量、视网膜电图、光学相干断层扫描 CT(眼睛、视网膜)等。检测指标分类使用频率(每种频率通过四舍五入,保留小数点后两位),见表 2。

高频的青光眼动物模型检测指标为眼压测量占 22.49%,组织病理检查占 12.59%,蛋白免疫印迹法检查占 12.22%,免疫组化检查占 11.98%,RGCs 计数占 9.41%、实时荧光定量占 7.70%、视网膜电图占4.77%,是评价青光眼动物模型成功的重

表 2　模型检测指标及使用频率

Table 2　Model detection indicators and usage frequency

检测指标 Detection index	频数(次) Frequency(times)	频率(%) Frequency(%)
眼压测量 Tonometry	184	22.49
组织病理(视网膜、视神经、眼球、房角) Histopathology (retina, optic nerve, eyeball, atrial angle)	103	12.59
蛋白免疫印迹(视网膜、眼睛、视网膜神经节、β-肌动蛋白、免疫球蛋白 G、RhoA、ROCK、Caspase-3) Western Blot (retina, eye, retinal ganglion, β-actin, immunoglobulin G, RhoA, ROCK, Caspase-3)	100	12.22
免疫组化(视网膜、视网膜视神经节、视神经、眼睛、脑、纤连蛋白、α 平滑肌肌动蛋白) Immunohistochemistry(retina, retinal optic ganglion, optic nerve, eye, brain, fibronectin, α smooth muscle actin)	98	11.98
RGCs 计数 RGCs count	77	9.41
实时荧光定量 Real-time fluorescence quantification	63	7.70
视网膜电图 Electroretinogram	39	4.77
光学相干断层扫描 CT(眼睛、视网膜) Optical coherence tomography CT(eye, retina)	34	4.16
电子显微镜(视网膜、视神经) Electron microscope (retina, optic nerve)	23	2.81
凋亡细胞检测 Apoptotic cell detection	22	2.69

续表 2

检测指标 Detection index	频数(次) Frequency(times)	频率(%) Frequency(%)
视神经轴突计数 Axon count of optic nerve	20	2.44
酶联免疫测(胶原蛋白 1、纤连蛋白、α-SMA、NO 水平、TGF-β 的浓度、血清 NLRP3、IL-6、IL-8、TNF-α、丙二醛(MDA)、超氧化物歧化酶(SOD)、TNF、IL-1β、MCP-1、血清 IgG、半胱天冬酶-3、硝基酪氨酸含量、TNF-α) Enzyme-linked immunoassay(collagen 1, fibronectin, α-SMA, NO level, TGF-β concentration, serum NLRP3, IL-6, IL-8, TNF-α, malondialdehyde(MDA), superoxide dismutase(SOD), TNF, IL-1β, MCP-1, serum IgG, caspase-3, nitrotyrosine content, TNF-α)	19	2.32
裂隙灯检查(眼睑、前房、眼球) Slit-lamp examination(eyelid, anterior chamber, eyeball)	15	1.83
线粒体 DNA 含量的测量、密度和大小定量、功能测定 Mitochondrial DNA content measurement, density and size quantitative, functional determination	8	0.98
房水流出检测 Aqueous humor outflow detection	8	0.98
定量逆转录聚合酶链反应乳酸脱氢酶测定 Quantitative reverse transcription polymerase chain reaction lactate dehydrogenase assay	5	0.61

要指标。在临床治疗中,眼压测量和视网膜形态是患者疾病发展和转归的重要参考依据,因此在未来的动物模型应用中,建议将眼压测量和视网膜形态改变作为重要指标考察,并参照临床检测标准制定符合青光眼动物模型的检测指标。

3 模型成功标准

目前,西医对于青光眼动物模型评价指标以病理指标、表观指标为主,经过对近 10 年青光眼动物实验统计分析拟定青光眼动物模型制备成功判断标准。具体见表 3。

表 3 青光眼动物模型成功判断标准

Table 3 Criteria for successful judgment of animal models of glaucoma

分类 Cassification	模型成功后趋势 Trend after model success
表观指标 Apparent index	眼压升高;房角形态改变(堵塞小梁网结构,正常虹膜形态消失);眼前节检查(裂隙灯下可见角膜钙化斑、虹膜色素脱失、瞳孔移位、眼前房内的房水混浊) Increased intraocular pressure; Changes in angular shape (blockage of trabecular mesh structure, disappearance of normal iris shape); Anterior segmental examination(corneal calcification spot, iris pigment loss, pupil displacement, and cloudy aqueous humor in anterior chamber can be seen under slit lamp)
病理指标 Pathological index	视网膜厚度及形态(视网膜各层组织均变薄、内丛状层厚度减少,内外核层融合为一层,细胞排列紊乱,神经节细胞明显减少) Retinal thickness and morphology(all retinal layers were thinner, the inner plexus layer was less thick, the inner and outer nuclear layers were fused into one layer, the cell arrangement was disordered, and the ganglion cells were significantly reduced)

4 讨论

青光眼是一种视神经病变,包括一系列神经退行性疾病,最终由于 RGC 功能障碍和退行性病变导致不可逆失明。青光眼属于中医“五风内障”的范畴,其代表不同的青光类型,绿风内障相当于原发性闭角型青光眼(primary angle-closure glaucoma, PACG),而青风内障类似于原发性开角型青光眼(primary open-angle glaucoma, POAG)[38]。本病的发生与脏腑、气、血、津液紊乱密切相关[39]。目前青光眼的临床护理标准是通过药物或手术方法降低 IOP 治疗;然而,即使 IOP 得到充分控制,眼压降低也不足以阻止患者的进行性视野丧失[40]。因此,迫切需要开发更安全有效的青光眼治疗方法[41]。青光眼的新治疗策略需要开发功能性的、可重复的、易于使用的、低成本的动物模型用于临床前研究。此外,这些模型应该模拟人类青光眼过程中出现的情况[42]。因此需要进一步的实验动物研究,为治疗药物筛选奠定基础。

综上所述,根据统计结果显示,目前研究者们较多选择的实验动物为 C57BL/6J 小鼠,性别多为雄性,造模方法以前房注射物质诱导型、转基因型、激光光凝诱导型最多。相关模型指标:检测眼压测量、组织病理、蛋白免疫印迹、免疫组化最多。青光眼动物模型发病机制复杂,目前研究结果表明青光眼发病过程中涉及 3 个功能类:线粒体、应激和核蛋白,表明在视网膜神经退行性过程中能量代谢、应激反应和基因表达改变的损伤[43]。因此可以考虑

从以上方面进行青光眼动物模型研究。理想的青光眼动物模型应能模拟人类青光眼的形态学、病理生理学及生化指标,具有类似的生物学机制,对其治疗药物有类似的药效反应,而以上模型尚不能达到此要求。但从解剖结构、生理功能及病理特点考虑,与西医青光眼定义与诊断存在较好的吻合度。目前中医病证结合的青光眼动物模型尚无统一标准,建议未来增加相关方面研究,更加有利于建立符合青光眼临床研究特点的实验动物模型与评估标准,将会有力推进中西医结合治疗青光眼的发展趋势[44]。

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